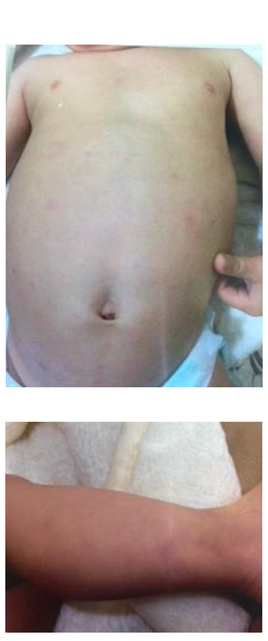
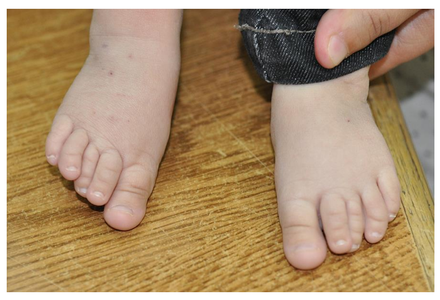
First reported cases of a novel variant of GNAS 1 gene

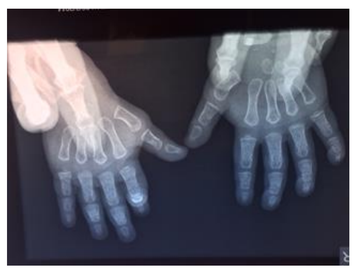
Olga Fafoula[1], Argyro Panagiotakou[2], Grigorios Grivas[1], Eleni Fryssira[3], Ioanna Kosteria[4], Paraskevi Korovessi[1], Stavroula Kostaridou[1]
[1]Pentelis Children's Hospital, Athens, Greece. [2]Departement of Endocrinology and Diabetes, Sismanoglio -Amalia Fleming Hospital, Athens, Greece. [3]Aghia Sofia Children's Hospital, Athens, Greece. [4]Health Center of Spata, Athens, Greece

Background: GNAS 1 gene (guanine nucleotide binding protein, alpha stimulating) encodes the alpha subunit of the stimulatory guanine nucleotide-binding protein (G-protein). Variations in the GNAS 1 can cause several disorders including Pseudohypoparathyroisism Type 1A (PHP1A), Type 1B (PHP1B), Type 1C (PHP1C), Pseudopseudohypoparathyroidism (PPHP), Progressive Osseous Heteroplasia (POH), and McCune-Albright syndrome (MAS).
Objectives: To report 2 patients, a father and his son who were identified to have the same pathogenic heterozygous GNAS1:c.1A>T variant in exon 1 of the GNAS1 gene.
Case Presentation: Our patient presented at the age of 4 months with a complaint of multiple cutaneous atrophies on his body. He was born at term, with IUGR and a weight of 2,145 kg after an IVF assisted conception. Laboratory tests showed an increased PTH, serum Phosphate in the upper limits and normal Calcium. A skin biopsy revealed dermal ossifications. Subsequently a GNAS genetic analysis identified a pathogenic heterozygous GNAS1:c1A>T variant in exon 1 of the GNAS1 gene. He is now 5 years old, with a short height of 96 cm (-3.0 SDS) and Weight of 14 Kg (-1.69). PTH, Calcium, and Phosphate measurements are within normal limits. IGF1 levels are low and GH provocations tests revealed normal GH secretion. Subsequently he developed hypothyroidism, and is now on thyroxine. Despite being hypotonic as an infant he has neurologically improved but still has dermal ossifications. Following the diagnosis, genetical analysis performed in both parents, revealed that the father carries the same variant. He is now 43 years old, has a height of 165 cm (-1,73 SDS), short fourth fingers and has been operated for scoliosis. At diagnosis he had an increased PTH, low 25 OH vitamin D, normal Calcium and Phosphate.

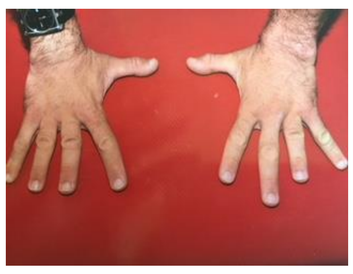
SON






FATHER

Conclusion: GNAS1: c.1A>T is a novel variant in exon 1 of the GNAS1 gene, not previously described. This substitution is predicted to disrupt the start codon (GNAS: p. Met1?). Heterozygous GNAS 1 inactivating variants cause pseudopseudohypoparathyroidism when paternally inherited. Although pseudopseudohypoparathyroidism mainly leads to Albright's Heretidary Osteodystrophy and not hormone resistance, our patient developed hypothyroidism. Further data is needed in order to establish the role of this novel variant in the clinical expression of the disease.

1. GNAS spectrum of disorders. S. Turan & M. Bastepe, Curr Osteoporos Rep 2015; 13(3): 146-158
2. Pseudohypoparathyroidism: diagnosis and treatment. G. Mantovani, JCEM 2011; 96(10): 3020-3030
3. The prevalence of GNAS Deficiency-Related Diseases in a Large Cohort of Patients Characterized by the EuroPHP Network. F.M. Elli et al, JCEM 2016; 101(10): 3657- 3668.
4. GNAS mutations and heterotopic ossifications. M. Bastepe, BONE 2018; 109: 80-85

57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018